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PREPARATION AND PROPERTIES OF SOME NEW TROPEINES

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XL.—*Preparation and Properties of some New Tropeines.*

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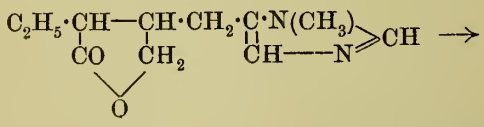
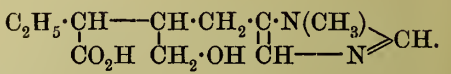
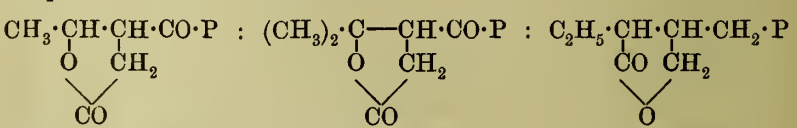
In the course of an investigation on the chemistry and pharmacology of the jaborandi alkaloids by one of us and Professor C. R. Marshall, it was shown (Trans., 1900, 77, 481) that, when caustic alkali is added to an aqueous solution of pilocarpine or *iso*pilocarpine, the specific rotatory power is diminished and that the minimum value is obtained when a molecular proportion of alkali has been added. The fact has also been observed (Marshall, *J. Physiol.*, 1904, 31, 153) that an aqueous solution of pilocarpine to which a molecular amount of caustic alkali has been added does not possess the characteristic physiological action of pilocarpine. Furthermore, it has been found that the specific rotatory power of pilocarpine in aqueous solution dropped from 100·5° to 77·5° simply on standing for three weeks; it has also been shown (Albertoni, *Arch. exp. Path. Pharm.*, 1879, 11, 415; Marshall, *loc. cit.*, 144) that, when instilled into the eye, aqueous solutions of the base are less active than solutions of a salt of similar strength. The explanation of these facts would appear to be that, under the above conditions, the lactone ring opens and the corresponding hydroxy-acid

or its salt is formed, and that the hydroxy-acid has a lower specific rotation and is less active physiologically than the lactone:



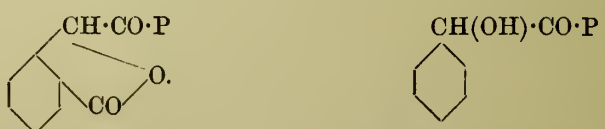


This connection between chemical constitution and physiological action derives additional importance from the fact that pilocarpine acts specifically on the so-called nerve-endings in the heart. It was therefore thought of interest to determine whether this difference in physiological action between a lactone and its corresponding hydroxy-acid could be observed in the case of other physiologically active bases. It has not been found possible, so far, to obtain a glyoxaline derivative similar to pilocarpine, and as atropine also acts on the nerve-endings of the heart, though antagonistically to pilocarpine, the tropeines were selected as suitable substances with which to investigate the difference in action between a lactone and its corresponding hydroxy-acid. For this purpose, it was decided to attempt the preparation of tropeines containing an acyl group similar to that existing in pilocarpine. Methylparaconyl- and terebyl-tropeines were therefore prepared, and the relation between these bases and pilocarpine is shown by the following formulæ, where P is the pharmacophore or nitrogen-containing complex:



Methylparaconyltropeine. Terebyltropeine. Pilocarpine.

In case these bases should prove to be physiologically inactive, an aromatic tropeine, similar to homatropine, but containing a lactone group, was also prepared. The relation between these bases is shown as under:



Phthalidecarboxyltropeine. Homatropine (mandelyltropeine).

At the same time it was thought of interest to investigate the physiological action of these and other tropeines and to determine to

what extent Ladenburg's generalisation applies. As the result of an investigation of the physiological action of a number of tropeines, this chemist has stated that the characteristic action of a tropeine, namely, its mydriatic action, depends not only on the presence of a tropine complex, but on the nature of the acyl group attached to it, which must contain (1) a benzene residue, (2) an aliphatic hydroxyl in the side-chain containing the carboxyl group. Thus, acetyl-, benzoyl-, and salicyl-tropeines do not produce mydriasis, but mandelyltropeine does. To test this generalisation further, we prepared glycollyl- and protocatechyl-tropeines in addition to those already mentioned. The present paper contains an account of the preparation and properties of these substances, as well as those of their principal salts. The physiological experiments conducted by Professor C. R. Marshall will be described in detail elsewhere, but a brief account of his results may now be given.

First, as regards the difference in action between a lactone and its corresponding hydroxy-acid, it has been found that both terebyl- and phthalidecarboxyl-tropeines, which produce an atropine-like effect on the heart, lose this action after a molecular proportion of alkali has been added to the base. They thus show, in aqueous and alkaline solution, a difference in action analogous to that observed in the case of pilocarpine.

As regards Ladenburg's generalisation that, to obtain a tropeine possessing mydriatic action, it is necessary to have the tropine complex attached to an acyl group containing an aromatic nucleus, it is found that this does not apply in the case of terebyltropeine. Whilst glycollyltropeine may be said to be inactive physiologically, terebyltropeine has a distinct mydriatic action, though very much weaker than atropine or homatropine.

Of the five tropeines examined, all were found, when tested on the vagus endings in the heart, to have an action similar in kind to that of atropine but—especially in the case of glycollyltropeine—very much weaker. The order of activity was as follows :

(1) Phthalidecarboxyltropeine,
(2) Terebyltropeine,
(3) Protocatechyltropeine,
(4) Methylparaconyltropeine,
(5) Glycollyltropeine,

the last on the list being very feebly active and much weaker than the rest. When applied to the eye in 1 per cent. solution (as a salt), the phthalidecarboxyl- and terebyl-tropeines both produced marked dilatation of the pupil, but both were very much weaker than either atropine or homatropine. The other three tropeines had no distinct mydriatic action.

The general results of this inquiry have proved, therefore :

(1) That the peculiar difference in physiological action between a lactone and its corresponding hydroxy-acid, as exemplified by pilocarpine and pilocarpic acid, also occurs in the case of a tropeine having a haptophore group similar to that in pilocarpine, namely, terebyltropeine, and also in the case of phthalidecarboxyltropeine.

(2) That Ladenburg's generalisation, so far as it refers to the necessity for a mydriatic tropeine to contain a benzene nucleus, does not strictly hold, since terebyltropeine possesses a distinct mydriatic action.

It would appear, however, that the conditions most favourable for the development of the mydriatic action in a tropeine are those stated by Ladenburg, namely, that the acyl group should contain a benzene nucleus and an aliphatic hydroxyl in the side-chain containing the carboxyl group.

Experimental.

Glycollyltropeine, $CH_2(OH)\cdot CO\cdot C_8H_{14}ON$.

This base was made by the general method devised by Ladenburg for the preparation of tropeines (*Annalen*, 1883, **217**, 82), namely, by neutralising tropine with glycollic acid and digesting the resulting solution with dilute hydrochloric acid (1 : 40) for twenty-four hours on a water-bath.

The crude base was purified by its conversion into the hydriodide and recrystallisation of this salt from methyl alcohol until pure. On regeneration, the base was obtained crystalline and was recrystallised from benzene until the melting point was constant; it formed laminar crystals melting at 113—114°, which are readily soluble in alcohol, moderately so in water, but dissolve only sparingly in ether.

0·11 gave 0·2436 CO_2 and 0·0864 H_2O. C = 60·4; H = 8·7.
$C_{10}H_{17}O_3N$ requires C = 60·3; H = 8·5 per cent.

The *hydrochloride* formed exceedingly deliquescent crystals, which, after drying at 110°, melted at 171—172°.

0·3644 gave 0·22 AgCl. Cl = 14·9.
$C_{10}H_{17}O_3N,HCl$ requires Cl = 15·0 per cent.

The *hydriodide* separated from methyl-alcoholic solution in stout, acicular crystals which melted at 187—188°; it is easily soluble in water, sparingly so in alcohol, and insoluble in ether. The salt contained half a molecule of water of crystallisation, which was not lost after five hours' heating at 110°, and at a higher temperature it became decomposed.

0·199 gave 0·1389 AgI. I = 37·7.
0·1987 gave 0·138 AgI. I = 37·5.
$(C_{10}H_{17}O_3N,HI)_2,H_2O$ requires I = 37·8 per cent.

The *nitrate* was obtained by the decomposition of the pure hydriodide with the requisite quantity of silver nitrate. It separated from its aqueous solution, on evaporation in a vacuum over sulphuric acid, as a viscid oil which gradually solidified. After recrystallisation from absolute alcohol, it was obtained in oblong, laminar crystals, which, after drying at 100°, melted at 120—121°.

0·2038 gave 0·3444 CO_2 and 0·1273 H_2O. C = 46·1; H = 6·9.
$C_{10}H_{17}O_3N,HNO_3$ requires C = 45·8; H = 6·9 per cent.

The *aurichloride* formed yellow, acicular crystals, which, after recrystallisation from hot water, melted at 186—187°.

0·2089 gave 0·0762 Au. Au = 36·5.
$C_{10}H_{17}O_3N,HAuCl_4$ requires Au = 36·6 per cent.

The *platinichloride* was not precipitated on the addition of the reagent to an aqueous solution of the hydrochloride. On evaporation, however, orange crystals were obtained, which separated from hot water in short, stout needles. After drying over sulphuric acid, the crystals melted and decomposed at 225—226°.

0·0595 gave 0·0145 Pt. Pt = 24·4.
$(C_{10}H_{17}O_3N)_2,H_2PtCl_6$ requires Pt = 24·2 per cent.

Methylparaconyltropeine, $CH_3\cdot\underset{\displaystyle O\cdot CO\cdot CH_2}{\overset{\displaystyle |}{C}}H—\underset{\displaystyle |}{C}H\cdot CO\cdot C_8H_{14}ON$.

This base, as well as the remaining tropeines described in this paper, was prepared by passing hydrogen chloride through a solution of tropine neutralised with the acid in question and maintained at a temperature of 120—125° for two to three hours (Täuber, D.R.-P. 95853). The dark brown gum thus obtained was decomposed by ammonia and the base extracted with chloroform; the crude tropeine was purified by conversion into the hydriodide. The pure base, regenerated from the purified hydriodide, was obtained as a colourless oil which refused to crystallise.

The *hydrobromide* separated from strong alcohol in square, laminar crystals which melted at 196—197°; this salt is anhydrous, and is easily soluble in water, but moderately so in absolute alcohol.

0·152 gave 0·2695 CO_2 and 0·0868 H_2O. C = 48·4; H = 6·3.
0·1942 „ 0·1057 AgBr. Br = 23·2.
$C_{14}H_{21}O_4N,HBr$ requires C = 48·3; H = 6·3; Br = 23·0 per cent

The *hydriodide* crystallised from alcohol in triangular groups of crystals, which, after drying in the air, melted at 177—178°; it is easily soluble in water, sparingly so in alcohol, and insoluble in ether.

0·178 gave 0·1054 AgI. I = 32·0.

$C_{14}H_{21}O_4N,HI$ requires I = 32·2 per cent.

The *aurichloride* was precipitated as a yellow oil, which solidified on rubbing with a glass rod. It was recrystallised from dilute hydrochloric acid containing a little alcohol, and thus obtained in the form of yellow, silky leaflets, which, after drying in the air, melted at 64—65°; this salt is moderately soluble in water and in alcohol.

0·1604, after drying at 100°, lost 0·0051 and gave 0·0504 Au. H_2O = 3·2; Au = 31·4.

$C_{14}H_{21}O_4N,HAuCl_4,H_2O$ requires H_2O = 2·9; Au = 31·5 per cent.

The *platinichloride* was obtained as an amorphous precipitate, and it separated from solution in dilute hydrochloric acid as a yellow powder which melted at 233—234°.

0·1002 gave 0·0206 Pt. Pt = 20·6.

$(C_{14}H_{21}O_4N)_2,H_2PtCl_6$ requires Pt = 20·7 per cent.

The *picrate*, after recrystallisation from alcohol, formed yellow, laminar crystals which melted at 190—191°.

Terebyltropeine, $\begin{matrix} CMe_2\text{-}CH\cdot CO\cdot C_8H_{14}ON \\ | \qquad\qquad | \\ O\cdot CO\cdot CH_2 \end{matrix}$.

This tropeine was prepared by a method similar to that employed in the case of methylparaconyltropeine, but the mixture was maintained at a temperature of 130—135° for two hours. The pure base, obtained through the hydriodide, solidified on standing, was dried on porous earthenware over sulphuric acid and recrystallised from acetone by the gradual evaporation of the solvent in a vacuous desiccator, and separated in small, diamond-shaped crystals which melted at 66—67°; it is very soluble in water or alcohol.

0·2086 gave 0·4892 CO_2 and 0·1542 H_2O. C = 64·0; H = 8·2.

$C_{15}H_{23}O_4N$ requires C = 64·1; H = 8·2 per cent.

The *hydrochloride*, which separated from its concentrated aqueous solution as a soft, crystalline mass, was drained on porous earthenware, and after two recrystallisations from acetone was obtained in the form of leaflets which softened at 80° and melted at 82°; it is very soluble in water or alcohol, but is insoluble in ether.

0·194 dried, first at 60° and then at 110°, lost 0·0196. $H_2O = 10·1$.
0·1722 dried at 110° gave 0·077 AgCl. Cl = 11·0.
$C_{15}H_{23}O_4N,HCl,2H_2O$ requires $H_2O = 10·2$.
$C_{15}H_{23}O_4N,HCl$ requires Cl = 11·2 per cent.

The *hydrobromide* separated from strong alcohol in small, laminar crystals which melted at 230—231°; it is easily soluble in water and moderately so in alcohol.

0·1927, dried at 110°, gave 0·1017 AgBr. Br = 22·5.
$C_{15}H_{23}O_4N,HBr$ requires Br = 22·1 per cent.

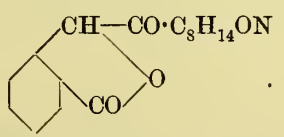
The *hydriodide*, after recrystallisation from alcohol, was obtained in the form of laminar crystals which melted at 213—214°; the salt is moderately soluble in water.

0·1986 gave 0·114 AgI. I = 31·1.
$C_{15}H_{23}O_4N,HI$ requires I = 31·1 per cent.

The *aurichloride* was precipitated as an oil which solidified after standing for several days; it was recrystallised from hot dilute hydrochloric acid and separated in imperfect crystals which melted indefinitely at 85—86°. The air-dried salt contains a molecule of water of crystallisation which is lost at 100°.

0·1324 air dried lost 0·0032 and gave 0·041 Au. $H_2O = 2·4$; Au = 31·0.
$C_{15}H_{23}O_4N,HAuCl_4,H_2O$ requires $H_2O = 2·8$; Au = 30·8 per cent.

The *platinichloride* separated as a gelatinous precipitate which could not be obtained crystalline. The *picrate* crystallised from dilute alcohol in yellow, matted leaflets which melted at 198—199°.

Phthalidecarboxyltropeine, 

This tropeine was prepared by a method similar to that employed in the case of methylparaconyltropeine, but the crude base was purified through the hydrobromide; it was recrystallised from ethyl acetate, and separated in square, laminar crystals which melted at 79—80°. It is very soluble in alcohol and moderately so in water or ether.

0·2028 gave 0·5037 CO_2 and 0·1195 H_2O. C = 67·7; H = 6·5.
$C_{17}H_{19}O_4N$ requires C = 67·8; H = 6·3 per cent.

The *hydrochloride* separated from absolute alcohol in laminar crystals which melted and decomposed at 242—244°.

0·1564 gave 0·0661 AgCl. Cl = 10·4.

$C_{17}H_{19}O_4N,HCl$ requires Cl = 10·5 per cent.

The *hydrobromide* was obtained in the form of glistening leaflets from alcohol, and, after drying over sulphuric acid, melted at 128—129°. The salt is readily soluble in water and contains a molecule of water of crystallisation.

0·1538 gave 0·2884 CO_2 and 0·0774 H_2O. C = 51·1 ; H = 5·6.

0·2014 ,, 0·0948 AgBr. Br = 20·0.

0·2028 ,, 0·0955 AgBr. Br = 20·0.

$C_{17}H_{19}O_4N,HBr,H_2O$ requires C = 51·0 ; H = 5·5 ; Br = 20·0 per cent.

The *nitrate* crystallises from water in square plates or in tufts of acicular crystals ; the air-dried salt contains water of crystallisation, and, after drying at 110°, melted at 169—171°. It is easily soluble in water or alcohol, but it is insoluble in ether.

0·1822 air dried lost 0·0087 H_2O. H_2O = 4·8.

0·1998 dried at 110° gave 0·4090 CO_2 and 0·1004 H_2O. C = 55·8 ; H = 5·6.

$C_{17}H_{19}O_4N,HNO_3,H_2O$ requires H_2O = 4·7 per cent.

$C_{17}H_{19}O_4N,HNO_3$ requires C = 56·0 ; H = 5·5 per cent.

The *aurichloride* crystallised from alcohol in golden-yellow leaflets which melted at 184—185°.

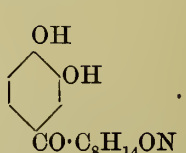
0·1776 gave 0·0546 Au. Au = 30·7.

$C_{17}H_{19}O_4N,HAuCl_4$ requires Au = 30·8 per cent.

The *platinichloride* was obtained as a yellow, amorphous powder which melted at 234—235°.

0·208 gave 0·0396 Pt. Pt = 19·0.

$(C_{17}H_{19}O_4N)_2,H_2PtCl_6$ requires Pt = 19·3 per cent.

Protocatechyltropeine, 

This tropeine was prepared by a method similar to that employed in the case of methylparaconyltropeine, but the crude base was purified by recrystallisation from absolute alcohol ; it separated in stout, acicular crystals which melted at 253—254° with decomposition. The base is sparingly soluble in water or alcohol.

0·1829 gave 0·4338 CO_2 and 0·1172 H_2O. C = 64·7 ; H = 7·1.

$C_{15}H_{19}O_4N$ requires C = 65·0 ; H = 6·9 per cent.

The *hydrochloride* crystallised from water in small, glistening plates or needles which did not melt below 300°; it is moderately soluble in water, sparingly so in alcohol, and insoluble in ether.

0·2027 gave 0·0944 AgCl. Cl = 11·5.

$C_{15}H_{19}O_4N,HCl$ requires Cl = 11·3 per cent.

The *nitrate* was so rapidly oxidised, either in solution or when exposed to the air, that it was not further investigated. The *aurichloride* separated as an amorphous precipitate which rapidly underwent reduction. The *platinichloride* separated from a hot solution in small, laminar crystals which melted at 228—229° with effervescence; it is sparingly soluble in water and almost insoluble in alcohol.

0·2019 gave 0·0404 Pt. Pt = 20·0.

$(C_{15}H_{19}O_4N)_2,H_2PtCl_6$ requires Pt = 20·2 per cent.

The *picrate* crystallised from alcohol in yellow plates which darkened at 255° and decomposed at 260—262°.

In conclusion, we wish to express our thanks to Professor A. W. Crossley for kindly supplying us with a quantity of pimelic acid, which was utilised for the preparation of terebic acid by the method described by Lawrence (Trans., 1899, **75**, 527).

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